Beneficial Effects of Atorvastatin on Lung Structural Remodeling and Function in Ischemic Heart Failure

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ABSTRACT

Background: Studies have suggested some benefit of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors in congestive heart failure (CHF), although the mechanisms remain uncertain. We hypothesized that statins could improve pulmonary hypertension and right ventricular function in ischemic CHF by reducing lung remodeling.

Methods and Results: Two weeks after myocardial infarct, rats received atorvastatin (n = 23) or no treatment (n = 23) for 3 weeks and were compared with a sham group (n = 16). Infarct size was similar by echocardiography and pathologic evaluations. Atorvastatin greatly reduced pulmonary hypertension and right ventricular hypertrophy: right ventricular systolic pressure 42 ± 5 vs. 28 ± 2 mm Hg (P < .01). Atorvastatin did not reduce left ventricular fibrosis and had minimal effects on left ventricular function. Right ventricular myocardial performance index was markedly improved by therapy (P < .01). CHF caused a restrictive lung syndrome with a downward shift of the respiratory pressure-volume loop, increased dry lung weight, and interstitial fibrosis that were greatly improved by atorvastatin. Reduced lung nitric oxide synthase expression was normalized by treatment. Atorvastatin also reduced isolated lung myofibroblasts proliferation after transforming growth factor–β stimulation (-36 ± 6%, P < 0.01).

Conclusions: 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibition reduces lung remodeling and dysfunction associated with heart failure with prevention of right ventricular hypertrophy and pulmonary hypertension. (J Cardiac Fail 2010;16:679–688)

Key Words: Drugs, lung, remodeling, heart failure, hypertension, pulmonary, pulmonary heart disease.

Pulmonary hypertension (PH) associated with congestive heart failure (CHF) reduces exercise capacity and carries a poor prognosis, especially when associated with right ventricular (RV) dysfunction.1–3 Although fluid overload and pulmonary edema no doubt contribute to the process, the mechanisms responsible for the pulmonary manifestations of chronic CHF involve both pulmonary vascular and alveolar septa structural remodeling.4,5

Among the less well-recognized pleiotropic effects of statins are the antiproliferative effects of these agents. Of particular importance, statins have demonstrated their capacity to reduce PH in animal models6 and to reduce connective tissue growth factor expression in human lung fibroblasts.7 Statin use is associated with a reduction of the decline in lung function associated with aging.8

Previous studies9–11 have led to conflicting data on the use of statin in patients with CHF, with some showing improved mortality and lower hospitalization rate, whereas others showed no benefit. The recently published results of the Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF (GISSI-HF) trial and of the Controlled Rosuvastatin Multinational Trial (ie, CORONA) evaluated the effect of rosuvastatin in patients with CHF12,13 and respectively suggested a reduction in hospitalization for CHF (CORONA) and no significant effect (GISSI-HF). None of these trials, however, was specifically designed to address the potential role of statins on pulmonary structural remodeling and lung function.

In this study, we evaluated the potential role of atorvastatin on pulmonary function, structural remodeling, PH, and right ventricular hypertrophy (RVH) in rats with CHF.
Methods

The study protocol was approved by the animal ethics and research committee of the Montreal Heart Institute and conducted according to guidelines from the Canadian council for the care of laboratory animals. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Experimental Protocol

Rats were submitted to myocardial infarction (MI) or sham surgery as previously described. To maximize the likelihood for the development of CHF with PH, only the animals with medium to large MI, evaluated by echocardiography 2 weeks after MI surgery, were included in this study. This was defined as LV wall motion abnormalities involving more than 25% of the segments evaluated in the basal and mid short-axis views. The rats with medium to large MI were randomly divided into 2 groups: MI + atorvastatin (Ator) (20 mg·kg⁻¹·d⁻¹ in food; n = 23) treatment group and MI group without treatment (n = 23). These therapies lasted for 3 weeks. The sham group received no treatment for the same period (n = 16).

Transthoracic Echocardiographic Study

LV and RV geometries and functions for all rats were performed at 2 and 5 weeks after MI surgery using a phased-array probe 10S (4.5-11.5 Megahertz) linked to a Vivid 7 system (GE Healthcare Ultrasound, Horten, Norway).15,16

In Vivo Respiratory Function Tests and Hemodynamic Measurements

All rats were anesthetized with xylazine (10 mg/kg) and ketamine (50 mg/kg). The trachea was isolated and connected to a computer-controlled, small-animal ventilator (FlexiVent, Scireq, Montreal, Quebec, Canada) to evaluate lung function. Lung compliance and elastance were determined and a respiratory pressure-volume loop was performed and analyzed using the Salazar-Knowles equation: $V = A - B \cdot e^{-K \cdot t}$ where A is the estimate of the inspiratory capacity, B equals total lung capacity − V (P = 0), and K is the curvature parameter. Afterwards, high-fidelity pressure catheters (Millar Instruments, Houston, TX) were inserted and advanced into the RV and LV to measure the hemodynamics using a powerlab polygraph System (AD Instrument, Colorado Springs, CO).

Lung and Heart Morphometric and Histological Measurements

The presence of pulmonary edema was evaluated by measuring the ratio of dry/wet lung weights of the right middle lobe. The left lung was perfusion fixed with OCT compound (Sakura, Torrance, CA) and frozen in 2-methylbutane prechilled with liquid nitrogen. To quantify collagen deposition in the lungs (n = 6 in each group) and noninfarcted LV tissue (n = 10, 11, and 9 in sham, MI, and Ator group, respectively), Masson’s trichrome staining was performed with standard protocols and was analyzed by the Image-pro Plus 6.2 software (Media Cybernetics, Bethesda, MD). The proportion of collagen deposition (stained in blue) was determined in 10 random visual fields per animal at 10× magnification.

The heart was removed and dissected. The left and right ventricles were separated and RVH was assessed by the ratio of the RV/LV + septum weights. For MI and MI + Ator rats, the LV scar was dissected and weighed and its surface area was determined by planimetry.

Protein Expression of endothelial nitric oxide synthase and Ser phospho-endothelial nitric oxide synthase

The lung tissue from sham (n = 4), MI (n = 5), and MI + Ator (n = 4) rats were homogenized and centrifuged. Western blotting analysis was described previously.17 Protein expression of phospho-endothelial nitric oxide synthase (p-eNOS) and total-eNOS (t-eNOS) were measured with the mouse anti-eNOS monoclonal antibody (1:1000; BD Transduction Laboratories). Phospho-eNOS was normalized to t-eNOS and t-eNOS was normalized to GAPDH (1:1000, Abcam).

Lung Myofibroblasts Proliferation

Lung myofibroblasts (MYFs) were isolated as previously described in details.18,19 First-passage cells from 10 different rats were grown to confluence and transferred into 96-well plates (200 cells in 200 μL). After 24 hours of starving, the media were changed to a serum-free media containing 2% penicillin-streptomycin, 1% Fungizone, and 0.2% insulin-transferrin-selenium and the cells were stimulated with insulin-transferrin-selenium medium only or with insulin-transferrin-selenium medium containing 10 ng/mL of transforming growth factor–β (TGF-β; Sigma), Ator (10 μM), or both. After 48 hours, the myofibroblasts proliferation was determined using the CyQuant (Invitrogen) cell proliferation assay as per the manufacturer’s instructions.

Statistical Analysis

All values are expressed as mean ± SEM. The 3 experimental groups were compared by one-way analysis of variance followed, when a significant treatment effect was found (P < .05), by the Fisher’s post hoc test for multiple comparisons. Percent change in myofibroblasts proliferation was evaluated by a Wilcoxon signed-rank test. Values of P < .05 were considered to be statistically significant.

Results

There was no mortality during the 3 weeks treatment period starting 2 weeks after MI in any study group. Baseline echocardiographic LV wall motion abnormality and wall motion score index were comparable between the MI and MI + Ator groups and remained similar at 5 weeks (Fig. 1). Infarct expansion measured from the ratio of scar weight and surface was also similar (Table 1).

Effects of Ator on Systemic Hemodynamics, LV Remodeling, and Function

Heart rate was comparable among all groups. There was decreased mean arterial pressure 5 weeks after MI that was not significantly affected by therapy. Compared with sham (10 ± 0.7 mm Hg), CHF increased in LV end-diastolic pressure at 5 weeks (23 ± 2 mm Hg) (P < .01). Ator reduced LV end-diastolic pressure to 15 ± 2 mm Hg (P < .01). Indices of LV contractility [(+dP/dt) and relaxation [(-dP/dt)] were reduced 5 weeks after MI and were improved by Ator (Table 1). Collagen deposition in noninfarcted LV (Fig. 2) was markedly induced in MI vs. sham rats (20.7 ± 1.8%...
vs. 1.4 ± 0.1%; P < .01) and was unaffected by Ator treatment (17.3 ± 3.0%).

LV echocardiographic parameters are presented in Table 2 with comparison of the absolute changes at 2 weeks and at 5 weeks. LV end-diastolic and end-systolic dimensions and LV end-diastolic and end-systolic areas were significantly increased in the MI group (P < .01 vs. change of sham). This was associated with depressed systolic function and significantly reduced LV (fractional shortening) (P < .01) in the MI group compared with the change of sham group. These parameters of LV remodeling and dysfunction were not significantly modified by Ator treatment.

Effects of Ator on Pulmonary Hemodynamics, RV Remodeling, and Function

Compared with sham (24 ± 1 mm Hg), CHF rats developed moderate PH with increased RV systolic pressure of 42 ± 5 mm Hg (P < .01). PH was markedly improved by Ator with a decrease to 28 ± 2 mm Hg (P < .01, Fig. 3A). At 5 weeks, RV end-diastolic pressure significantly increased to 4 ± 1 mm Hg in the MI groups (P < .01 vs. sham 0.9 ± 0.3 mm Hg). Ator decreased RV end-diastolic pressure to 1.6 ± 0.4 mm Hg (P < .01, Fig. 3B). CHF induced RVH with RV/LV + septum weights ratio of 40 ± 4% compared with 22 ± 0.5% in the sham group (P < .01). Ator nearly normalized RVH down to 29 ± 2% (P < .05, Fig. 3C).

RV echocardiographic parameters are presented in Table 3. RV echocardiography demonstrated trends toward increased RV end-diastolic dimension, tricuspid valve closing to opening time (TVc-o) and decreased RV ejection time (RVET) in the MI compared with the sham group, which were improved by Ator treatment. Moreover, RV myocardial performance index (RVMPI), calculated as of RVMPI = (TVc-o – RVET)/ RVET, represents an index of both systolic and diastolic function and was greatly increased (worse function) in CHF (P < .05) and markedly improved by Ator (P < .01). Furthermore, RV systolic function measured by tricuspid annulus plane systolic excursion was significantly reduced in the MI group and was improved by Ator (P < .01).

Effects of Ator on Pulmonary Structural Remodeling and Function

The wet lung/body weight ratio increased by 62% after MI (P < .01) and Ator markedly improved this ratio (P < .05, Fig. 4A). Similarly, the dry lung/body weight ratio was increased by 70% after MI (P < .01), providing evidence of substantial pulmonary remodeling: treatment with Ator reversed this increased ratio (P < .05, Fig. 4B). The dry/wet lung weight ratio was comparable among all groups, suggesting that no significant edema occurred (Fig. 4C). The lung tissue collagen deposition (Fig. 5) was greater in MI than in sham rats (14.1 ± 1.8% vs. 4.6 ± 0.4%; P < .01). Ator-treated rats had a level comparable to that of sham rats (4.4 ± 0.7%). Pulmonary function was significantly reduced by CHF and markedly improved by Ator (Table 1). CHF caused a restrictive lung syndrome with a downward shift of the

![Fig. 1](image-url)
lungs pressure-volume loop, which was greatly improved by Ator (Fig. 6). A decreased value of the shape constant K reflects downward concave shape of the inflation curve of the pressure-volume loop. The total inspiratory capacity (A) as well as the total lung capacity minus the volume at pressure 0 (B) were reduced in CHF and normalized by Ator (Fig. 6).

Lung total eNOS protein expression was reduced after MI ($P < .01$) and was normalized by Ator therapy ($P < .05$, Fig. 7). There was no difference in phospho-eNOS expression between groups. Isolated lung myofibroblasts proliferation ($n = 10$) was reduced by Ator in both basal conditions and after stimulation by TGF-$\beta$ ($P < .01$, Fig. 8).

**Discussion**

We evaluated the effects of Ator on lung structural remodeling and function in rats with ischemic heart failure. CHF

| Table 1. Effect of Atorvastatin on Hemodynamic, Morphometric, and Respiratory Function Parameters |
|-------------------------------------------------|-----------------|-----------------|
| HR (beats/min) | 272 ± 16 | 257 ± 13 | 288 ± 15 |
| MAP (mm Hg) | 97 ± 4 | 85 ± 4* | 92 ± 3 |
| LVEDP (mm Hg) | 10 ± 0.7 | 23 ± 2 | 15 ± 2 |
| LV (+)dP/dt (mm Hg/s) | 8511 ± 519 | 5182 ± 371$^1$ | 6658 ± 474$^{1+}$ |
| LV (-)dP/dt (mm Hg/s) | 5821 ± 378 | 3107 ± 282$^1$ | 4169 ± 268$^{1+}$ |
| RV (+)dP/dt (mm Hg/s) | 1338 ± 86 | 1650 ± 137 | 1442 ± 100 |
| RV (-)dP/dt (mm Hg/s) | 813 ± 44 | 1102 ± 108$^*$ | 924 ± 82 |
| BW (g) | 403 ± 6 | 398 ± 8 | 402 ± 5 |
| Scar weight (g) | N/A | 0.10 ± 0.01$^1$ | 0.10 ± 0.01$^1$ |
| Scar surface (mm$^2$) | N/A | 0.03 ± 0.00$^1$ | 0.03 ± 0.00$^1$ |
| Scar weight/surface (g/mm$^2$) | N/A | 94.8 ± 8.0$^1$ | 95.3 ± 8.4$^1$ |
| Respiratory compliance (mL/cmH$_2$O) | 1.26 ± 0.04 | 0.95 ± 0.09$^1$ | 1.21 ± 0.05$^1$ |
| Respiratory elastance (cmH$_2$O/mL) | 0.83 ± 0.03 | 1.43 ± 0.21$^1$ | 0.87 ± 0.04$^1$ |

Ator, atorvastatin; HR, heart rate; MAP, mean arterial pressure; LV, left ventricular; RV, right ventricular; LVEDP, LV end-diastolic pressure; BW, body weight; MI, myocardial infarction.

* $P < .05$ vs. sham.

† $P < .01$ vs. sham.

$^1$ $P < .05$ vs. MI.

$^2$ $P < .01$ vs. MI.

**Fig. 2.** Effect of atorvastatin (Ator) on noninfarcted left ventricular (LV) structural remodeling assessed by Masson’s trichrome staining for collagen in blue (upper pictures) and by quantitative analysis for LV collagen deposition (lower graph) in sham, myocardial infarction (MI) rats, and MI + Ator rats. Results are expressed as mean ± SEM. * $P < .01$ vs. sham.
induced lung dysfunction and important structural remodeling characterized by excessive collagen deposition. This pulmonary restrictive syndrome was associated with the development of PH, RV dysfunction and RVH. Therapy with Ator reduced lung structural remodeling, improved lung dysfunction, and also prevented PH and RVH. These benefits occurred despite similar baseline infarct size and degree of LV dysfunction. Ator had minimal effects on LV remodeling and function as scar size, noninfarcted LV collagen deposition, and echocardiographic parameters of LV function remained largely unchanged 3 weeks later. Mechanistically, Ator normalized increased lung eNOS protein expression and reduced basal and stimulated lung

Table 2. LV Echocardiographic Parameters

<table>
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<tr>
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<th>Sham</th>
<th>MI</th>
<th>MI + Ator</th>
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<tr>
<td>2 Weeks</td>
<td>2 Weeks</td>
<td>5 Weeks</td>
<td>Change</td>
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<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>7.2 ± 0.1</td>
<td>7.4 ± 0.2</td>
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<td>LV end-systolic dimension (mm)</td>
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<td>3.56 ± 0.17</td>
<td>(-) 0.07 ± 0.12</td>
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<td>RVSP (mmHg)</td>
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<td>78.0 ± 2.3</td>
<td>0.2 ± 0.8</td>
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<td>RVEDP (mmHg)</td>
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<td>48.8 ± 2.4</td>
<td>0.2 ± 0.8</td>
</tr>
<tr>
<td>FAC (%)</td>
<td>66.3 ± 1.8</td>
<td>66.3 ± 1.8</td>
<td>0.2 ± 0.8</td>
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<tr>
<td>LV end-diastolic area (mm²)</td>
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<td>64.4 ± 2.1</td>
<td>0.2 ± 0.8</td>
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<tr>
<td>LV end-systolic area (mm²)</td>
<td>16.7 ± 1.3</td>
<td>16.7 ± 1.3</td>
<td>0.2 ± 0.8</td>
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<td>2 Weeks</td>
<td>5 Weeks</td>
<td>Change</td>
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<tr>
<td>LV end-diastolic dimension (mm)</td>
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<td>0.2 ± 0.1</td>
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<tr>
<td>LV end-systolic dimension (mm)</td>
<td>3.6 ± 0.16</td>
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<tr>
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<tr>
<td>FAC (%)</td>
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<td>66.3 ± 1.8</td>
<td>0.2 ± 1.8</td>
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<tr>
<td>LV end-diastolic area (mm²)</td>
<td>64.4 ± 2.1</td>
<td>64.4 ± 2.1</td>
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<tr>
<td>LV end-systolic area (mm²)</td>
<td>16.7 ± 1.3</td>
<td>16.7 ± 1.3</td>
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Fig. 3. Effect of atorvastatin (Ator) on (A) right ventricular systolic pressure (RVSP), (B) right ventricular end-diastolic pressure (RVEDP), and (C) right ventricular hypertrophy (RVH) after treatment in sham, myocardial infarction (MI), and MI + Ator rats. Results are expressed as mean ± SEM. *P < .01 vs. change of sham. †P < .05 vs. MI; ‡P < .01 vs. MI.
myofibroblasts proliferation. These data suggest some direct beneficial effects of Ator on pulmonary function in CHF.

Among the less well-recognized pleiotropic effects of statins are the antiproliferative effects of these agents. These effects are the result of direct inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase leading to a reduced production of the isoprenoid intermediates of cholesterol biosynthesis farnesylpyrophosphate and geranylgeranylpyrophosphate.

Effects of Ator on Lung Structural Remodeling and Function

The repair process in response to lung injury is characterized by the proliferation of MYFs that can originate from resident lung cells or from marrow derived cells. MYFs contribute to lung remodeling and fibrosis in animal models of lung fibrotic disease as well as to the alveolar wall thickening, fibrosis, and restrictive lung syndrome found in animal models of CHF. In human postcapillary pulmonary hypertension, Kapanci et al previously demonstrated alveolar septa proliferation of MYFs, nonobservable in precapillary pulmonary hypertension.

Conceptually, MYF proliferation and fibrosis could play an initially protective role against the insulting increase in capillary pressure and prevent the development of alveolar edema. In the longer term, however, this response likely becomes maladaptive and contributes to a restrictive lung syndrome, PH, and RVH. In another study, we also demonstrated that mRNA levels of collagen, fibronectin, and TGF-β1 and TGF-β3 were elevated in these lungs. Watts et al demonstrated that simvastatin-modulated connective tissue growth factor expression via a Rho signaling pathway in human lung fibroblasts connective tissue growth factor is a fibroblast mitogen and promoter of collagen deposition. In this study, we found excessive collagen deposition and downregulated eNOS protein expression in the lungs of CHF rats; both were reversed by Ator therapy. In support of these findings, a previous study demonstrated that CHF depressed pulmonary artery eNOS expression. It is therefore possible that statins effectively attenuate the maladaptive lung structural remodeling associated with heart failure through Rho kinase and eNOS pathways. It has indeed been suggested that the regulation of eNOS by Rho GTPases may be an important mechanism underlying the cardiovascular protective effect of statins. Phosphorylation of Ser1177 eNOS

### Table 3. Right Ventricular Echocardiographic Parameters

<table>
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<th>MI+Ator</th>
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<td><strong>5 Weeks</strong></td>
<td><strong>Change</strong></td>
<td><strong>2 Weeks</strong></td>
</tr>
<tr>
<td>RVDd (mm)</td>
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<td>3.5 ± 0.1</td>
<td>(+) 0.1 ± 0.1</td>
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<tr>
<td>RVET (ms)</td>
<td>85.3 ± 1.2</td>
<td>84.5 ± 2.3</td>
<td>(–) 0.8 ± 2.3</td>
</tr>
<tr>
<td>TVc-o (ms)</td>
<td>86.1 ± 2.0</td>
<td>87.8 ± 2.8</td>
<td>(+) 1.7 ± 2.5</td>
</tr>
<tr>
<td>RVMI</td>
<td>0.01 ± 0.02</td>
<td>0.04 ± 0.02</td>
<td>(+) 0.03 ± 0.03</td>
</tr>
<tr>
<td>TAPSE</td>
<td>3.0 ± 0.1</td>
<td>3.3 ± 0.1</td>
<td>(+) 0.3 ± 0.2</td>
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*P < .05 vs. change of sham. 
1P < .01 vs. change of sham. 
2P < .01 vs. change of MI.

Fig. 4. Effect of atorvastatin (Ator) on (A) wet lung/body weights, (B) dry lung/body weights, and (C) dry/wet lung weights ratios after treatment in Sham, myocardial infarction (MI), and MI + Ator rats. Results are expressed as mean ± SEM. *P < .01 vs. sham; †P < .05 vs. MI.
may also play an important role in the activity of this enzyme. Although total eNOS was reduced in CHF and increased by Ator therapy, we did not find any difference in the proportion of phospho-eNOS expression, suggesting that this phosphorylation site does not contribute to modification of eNOS activity in CHF and with statin therapy.

**Fig. 5.** Effect of atorvastatin (Ator) on pulmonary structural remodeling assessed by Masson’s trichrome staining for collagen in blue (upper pictures) and by quantitative analysis for lung collagen deposition (lower graph) in sham, myocardial infarction (MI) rats, and MI + Ator rats. Results are expressed as mean ± SEM. *P < .01 vs. sham; †P < .01 vs. MI.

**Fig. 6.** Effect of atorvastatin (Ator) on respiratory function by pressure-volume (P-V) loops technique after treatment in sham, myocardial infarction (MI), and MI + Ator rats. A decreased value of K reflects downward concave shape of the inflation curve of the P-V loop. A reflects the total inspiratory capacity and B reflects the total lung capacity minus the volume at pressure 0. Results are expressed as mean ± SEM. *P < .05 vs. sham; †P < .01 vs. Sham; ‡P < .01 vs. MI.
Quasi-static respiratory system compliance was measured as a nonspecific indicator of lung injury, and respiratory pressure-volume loops were obtained 5 weeks after MI. CHF caused a reduced respiratory compliance and a downward shift of the respiratory pressure-volume relation. This was markedly improved by Ator therapy. Alveolar septal thickening is also likely responsible for the impaired pulmonary gas diffusing capacity seen in the subjects with CHF, both at rest and during exercise. It is therefore plausible that statin therapy could improve gas exchange, reduce dyspnea, and increase exercise capacity through this mechanism.

MYF proliferation and excessive collagen deposition in the lung contribute to the development of PH and RVH. Statins have demonstrated their capacity to reduce PH in animal models of pulmonary arterial hypertension and to reduce connective tissue growth factor expression in human lung fibroblasts. Our in vitro findings that Ator could reduce basal and TGF-β-stimulated lung myofibroblasts proliferation further supports that CHF lung could be a direct pharmacological target of statins. A recent study further suggests that statin use is associated with a reduction of the decline in lung function associated with aging. This antifibrotic action of statin in lungs could eventually reduce the development of PH and RVH and improve RV structural remodeling and RV function.

Effects of Ator on RV and LV Function and Remodeling

Ator improved RV function as measured by both the RVMPi and tricuspid annulus plane systolic excursion. Ator also partly attenuated the severity of the hemodynamic impact of CHF with significant lowering of LV end-diastolic pressure and increase of LV (±) dP/dt. There were, however, no effects on scar size, on noninfarcted LV collagen deposition, and on LV function and geometry as evaluated by echocardiography. In a previous study, the angiotensin receptor blocker Irbesartan administered early after MI (48 hours) also reduced lung remodeling to a similar extent with improvement of LV contractility and function. It is therefore possible that some beneficial effects on lung function observed in this study were partially due to improvement in LV contractility and hemodynamics.

Fig. 7. Effect of atorvastatin (Ator) on lung phospho-eNOS and total-eNOS protein by western blotting in sham, myocardial infarction (MI), and MI + Ator rats. Results are expressed as mean ± SEM. *P < .01 vs. sham; †P < .05 vs. MI.

Fig. 8. Effect of atorvastatin, transforming growth factor-β, or both on isolated lung myofibroblasts proliferation. All changes are significant at P < .01.
Basic and Clinical Relevance of this Study

In summary, our findings demonstrate that Ator therapy in CHF is associated with reduced lung remodeling, reduced PH and lung fibrosis, and improved respiratory and RV function. Although some of these effects could be due to direct improvement of LV function, we also provide direct evidence that Ator reduces lung myofibroblasts proliferation and normalizes lung eNOS expression. Thus, direct effects of Ator on lung remodeling could play a significant role in the improvement of respiratory and RV functions.

Use of rat MI model in the development of drugs for the therapy of CHF has been validated. Two large randomized trials evaluated statins in CHF. The GISSI-HF trial suggested that rosuvastatin showed no effect on clinical outcomes in patients with symptomatic CHF. However, the population consisted mostly of nonischemic cardiomyopathy. The CORONA trial enrolled older patients with ischemic heart failure and showed that rosuvastatin reduced the number of cardiovascular hospitalizations, which is consistent with Go and Foody’s studies. In these trials, there was no a priori evaluation of respiratory function and pulmonary pressure. Although there is evidence that chronic human CHF is associated a restrictive lung syndrome and reduced gas diffusion capacity, the time scale of these events in man in currently unknown. The important remodeling observed only 2 weeks after MI in rats could be specific to that model.

Conclusions

Rats with ischemic CHF developed moderate PH and important lung structural remodeling characterized by excessive collagen deposition and associated with RV dysfunction and RVH. These changes are reversed by therapy with Ator despite similar infarct size. This observation provides an additional possible mechanism by which statins may exert beneficial effects in CHF: some of the effects may be directly on the lungs. These findings should be considered in the design of future clinical trials evaluating statins in CHF.

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Disclosures

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